

SEIR with Pulse Control Measures: A Model for the 2014 West Africa Ebola Epidemic

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1 Summary

This paper defines a model that could be used to evaluate the effectiveness of control measures during the West Africa Ebola epidemic. The introduction gives a general background of the outbreak, an overview of the disease in context, and common modes of regional travel.

A brief introduction of compartmental models is given, emphasizing parameters useful in modeling. Two major factors are addressed: the declining effectiveness of traditional control and the possible benefit of increased monitoring and intermittent house-level quarantine.

2 Purpose

This model has been formulated to aid implementation of the Sierra Leone Government's control measures, specifically the development of a national surveillance program combined with rolling lockdown.

Although a large scale Ebola epidemic has never been controlled in this manner, the hypothetical effect may be inferred from the fact that the host species and humans have historically cohabited without a widespread epidemic, or reported outbreak, in West Africa.¹

Further, experience has shown that calls for international assistance are not necessarily heeded in a timely or effective manner, and that the capacity to stop the spread of the disease through conventional measures is not scaling with the course of the epidemic.

¹ Derek J. Taylor, Matthew J. Ballinger, Jack J. Zhan, Laura E. Hanzly, and Jeremy A. Bruenn. Evidence that ebolaviruses and cuevaviruses have been diverging from marburgviruses since the miocene. *PeerJ*, 2:e556, 9 2014. ISSN 2167-8359. doi: 10.7717/peerj.556. URL <http://dx.doi.org/10.7717/peerj.556>

3 Background

The first identified case died on December 6th, 2013, in Meliandou Village, Guéckédou Prefecture, Guinea.² Before being identified as *Zaire Ebola virus* (ZEBOV), the outbreak spread to Macenta prefecture around March 7th. The disease was identified by Médecins sans Frontières (MSF) from samples taken in mid-March. In early April, the outbreak spread to Conakry, a major urban center and the capital of Guinea. In early June, outbreaks were reported in Téliélé and Boffa prefectures in Guinea, Kailahun and Kenema Districts in Sierra Leone, and Lofa and Montserrado counties in Liberia.

² Baize et al., 2014

The outbreak is the largest cluster of Ebola cases on record. Although previous outbreaks of ZEBOV have seen fatality rates as high as 90%, a rough figure of the fatality rate of this strain of ZEBOV is 60%. The incubation period is approximately five days, but can range from 3-21 days. The infective period is approximately five days. The greatest risk of infection is from very sick individuals and the dead.

3.1 Ebola in West Africa

Possible reservoirs include fruit bats of the species *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*, which have historically existed in a belt across the whole of West Africa. Genetic analysis performed on samples from 78 individuals in Sierra Leone showed no evidence of additional exposure from animals sources, beyond the first case.³

³ Gire et al., 2014

Phylogenetic analysis⁴ estimates the mutation of this strain occurring sometime around 2002. Recent analysis of samples collected at the Lassa Diagnostic Laboratory in Kenema between 2006–2008 showed that 8.2% (18/219) of patients received with acute illness, having tested negative for malaria, tested positive for EBOV (Zaire-76 strain) activity.⁵ This data should be qualified by the fact that the data is a non-random sample.⁶ That is, despite being drawn from 219 samples, the data may not be indicative of the general population.

⁴ Dudas G, 2014

⁵ Schoepp et al., 2014

⁶ rather than random, it is individuals who sought care at a health clinic, showed signs of hemorrhagic fever, followed a referral, and then tested negative for malaria

A study of immune responses in epidemic and non epidemic regions of Gabon was published in 2010.⁷ The study sampled 4,349 individuals in 220 randomly selected villages, finding a 15.5% average of specific anti-ZEBOV IgG immune responses. Spatial variation of the resistant fraction correlated strongly with landuse, with the highest levels (19.4%) found in forested areas. It was speculated that the correlation is the result of conduciveness of the environment to bats, and that some non-lethal exposure is transmitted from fruit. Specifically the authors note in the discussion: "Thus, it is possible that ZEBOV antigenic stimulation or aborted infection could occur when villagers handle and eat fruits which have been contaminated by bat saliva that may contain infectious virus,

⁷ Becquart et al., 2010

inactivated virus, or simple viral antigens. Brief contact with non-infectious viral particles is sufficient to induce the type of specific immunity observed in our study." The study also noted a linearly increasing immune response with age, indicating that children may be particularly vulnerable. The antibodies most commonly found in the study were active towards the proteins (VP40 & NP), which are multi-functional components critical in reproduction and self-assembly of the virus.

3.2 Travel

On the available mobility within the region, the road network in Guinea is well developed by regional standards, both in terms of road condition and overall system implementation. The road networks in Sierra Leone and Liberia suffered from neglect during the conflict of the 1990s and lingering set-backs to governance, civil-society and investment in the decade following. A number of major road infrastructure projects were on-going in Sierra Leone and Liberia to improve access to rural areas. The outbreak is currently showing the most alarming growth in Liberia, in Lofa County and the capital Monrovia. Controlling transmission in a mobile population, located in a remote area, with a high level of cross-border trade has proven challenging.

Public transport is typically provided by modified mini-buses carrying up to 21 people in space intended for eight. Fuel subsidies make travel accessible to average citizens, with travel across an urban area in this manner costing as little as \$0.25 USD, and regional transport (Freetown–Kailahun) costing around \$15 USD.

In rural areas, inexpensive (\$1,250) small displacement Chinese-made motorcycles have become increasingly ubiquitous. They can carry three to four people, market goods and even livestock. A ten kilometer trip costs a single passenger about \$1.25 USD one way.

3.3 Compartmental Models

Basic compartmental models describing the transmission of communicable diseases as grouped populations were first outlined by Kermack–McKendrick⁸.

In brief, compartmental models attempt to quantify the number of individuals in various phases of infection with differential equations.

Legrand's *Susceptible-Exposed-Infectious-Hospitalized-Funeral-Resistant* (SEIHFR) model⁹ is a compartmental model developed specifically for Ebola. Parameters for the transmission of different strains of *Ebola virus* (EBOV) in different historical situations were also developed. Of key interest is the transmission coefficients for funerals, community activity and hospitals. Specifically, assuming a two day traditional burial period, the contact factor for traditional funerals was roughly eight times higher than transmission in the community and hospitals combined. And that after effective med-

⁸ Kermack and McKendrick, 1991

⁹ Legrand et al., 2007

ical intervention, the transmission coefficients for hospitals and funerals is effectively zero.

4 Working Hypothesis: Endemic-Shift

HYPOTHESIS: EBOLA HAS PREVIOUSLY EXISTED IN A STABLE ENDEMIC CONDITION IN WEST AFRICA, HOWEVER DUE TO FUNDAMENTAL AND PERVASIVE CHANGES TO THE NATURE OF THE TRANSMISSION NETWORK, NEW OUTBREAKS HAVE THE POTENTIAL TO BECOME LARGE-SCALE EPIDEMICS.

It is hypothesized here that the epidemic occurred due to the wide availability of cellular communication, inexpensive transportation and improved access to health-care facilities. That is, the ability to call relatives in neighboring villages, the ability of relatives to travel, access to multiple trained rural health-care workers and the ability of those individuals to seek medical attention in a local hospital (super-spreading event) were all crucial elements in the initial outbreak. They are also factors which have seen dramatic increases in recent years.

In a compartmental model scale, a low reproduction ratio (marginally above one) in rural areas may indicate that increased mobility and population density may be contributing factors.

If a pre-existing immune response provides some level of resistance or has a significant effect on mortality, then changes in land use and public behavior may also be contributing factors. Given the *hard-won evidence* on the development of immune responses (VP40,NP,VP35,GP) in endemic and non-endemic regions¹⁰, the development^{11,12} of effective Ebola vaccines based on exposure to virus like particles (VLP)s (inducing VP40,NP,GP responses), and the effectiveness and safety profile of those vaccines in non-human primates (NHP)¹³, some public health recommendations which confuse reported or proven pathways of lethal exposure with likely sources of VLPs may be in need of review.

A pre-existing immune response may either be full immunity or a key factor in ultimate outcome. Since burials are often crucial in the transmission chain, a marginal decrease in fatality has a disproportionate on transmission effect.

Four possible scenarios immediately present themselves as transitions to a new endemic stability state:

1. Improved Treatment,¹⁴ increasing the fraction of resistant population members with a more acceptable causality rate. Unless the treatment can be administered quickly or self-mediated, it is not likely to be scalable.
2. Vaccination,¹⁵ with priority given to consenting healthcare workers and their families, and preference to viable options with proven efficacy and good safety profiles in NHPs.

¹⁰ Becquart et al., 2010

¹¹ Warfield and Aman, 2011

¹² Warfield et al., 2007

¹³ Warfield et al., 2014

¹⁴ specifically antibody serums or blood transfusions from *recent* survivors and/or early treatment schemes

¹⁵ Galvani et al., 2014

3. Epidemic, loss of approximately 40%-60%¹⁶ of the current population to the disease itself.¹⁷
4. An Ebbing Endemic, a wavelike progression of cases controlled by a β near the critical level, or an oscillating β reflecting effectiveness of control measures and changes in public behavior.

Proper sampling of immunity (by random sampling, capturing both the regional variation and uncertainty) is proposed to determine the extent of the disease prevalence in the region and the required increase in resistant fraction. From the Gabon study¹⁸, the linear increase to age ten, and the leveling of immune response beyond suggests a waning immunity in steady state. From this, it may also be necessary to sample individuals in time. Dual species Geographic Information System (GIS) compartmental epidemiological models have been proposed¹⁹ to study the dynamics of the disease with the host species. The development of vaccines with antigen specific groups of VLPs suggests techniques capable of characterizing specific antigens should be used, such as Western blot analysis. The development of raster population density maps and methods to quantify movement are a likely by-product of more sophisticated analysis being undertaken.

Assuming that the connectedness of individuals will continue to increase as the region is developed, then some fraction of the region will require resistance to ZEBOV as some function $f(\beta)$, where β will likely continue to increase as the region develops.

5 SEIR as Partial Quarantine with Pulse Control

A simplification of Legrand's model for the current situation would be to consider a *Susceptible-Exposed-Infected/Funeral-Resistant* model, where quarantined individuals move to the resistant class but a fraction proceeds with an unaltered contact rate. The infective class here encompasses both individuals who are infected, as well as those who succumb to the disease and are buried in a traditional manner. The infection rate approaches a limit as the unquarantined infected fraction increases.

Taking both quarantined and unquarantined cases together results in a reproduction ratio above zero but less than the uncontrolled rate, $\mathcal{R}_{controlled} \approx 0$, $\mathcal{R}_{controlled} < \mathcal{R}_{effective} < \mathcal{R}_{uncontrolled}$.

Legrand found a basic reproduction ratio of 2.7 (95% CI 1.9–2.8) using a stochastic model. However, fitting a deterministic SEIR model to the initial outbreak indicates an $\mathcal{R}_{uncontrolled}$ of 1.18, with an initial $\mathcal{R}_{effective}$ of 0.9 after interventions by MSF. This may be attributed to the nature of the transmission network and be better explained by recent methods developed for hybrid network/compartmental analysis.

Following spread to Sierra Leone and Liberia, the $\mathcal{R}_{effective}$ increased to around 1.24 overall for several months. After the collapse of control measures in Monrovia, the regional overall $\mathcal{R}_{effective}$ has

¹⁶ rough estimate assuming a period of uncontrolled spread, homogeneous mixing, followed by complete social & economic collapse

¹⁷ the "do nothing" case, or any approach which does reverse the course of epidemic and cannot scale for practical reasons.

$\mathcal{R}_0$	p
1.2	16.6%
1.4	28.6%
1.6	37.5%
1.8	44.4%
2.0	50.0%
2.4	58.3%
2.8	64.3%
3.0	66.7%
3.5	71.5%
4.0	75.0%
5.0	80.0%

Table 1: Required immune fraction

¹⁸ Becquart et al., 2010

¹⁹ Olival and Hayman, 2014

increased to $\approx 1.8 - 1.9$. This model estimates the progression of the infection rate as a logistic regression, where β approaches some value β_{max} as a function of the infected population.

Continued transmission implies some unquarantined fraction. Unreported cases are not counted in this model. However, the unquarantined contact rate together with the current rate of new cases (βSI) may be used to estimate the size of the unreported population at some prior time which would lead to a later rate of new cases. While, the true extent of unreported cases may be that of compounding series²⁰, which is not yet treated in this approach.

$$^{20} \sum_{n=0}^{\infty} n \sigma_I = \left(\frac{1}{\sigma_I} - 1 \right)^{-1}?$$

In addition to the above assumptions, changes in public behavior are difficult to estimate and quantify. And spatial variation can have marked effect on contact rates, e.g. between urban and rural environments. The progression of the epidemic at different rates in different environments presents a complex hazard.

Using the standard *Susceptible-Exposed-Infected-Resistant* SEIR model, with a separate class for deaths,

$$\frac{dS}{dt} = S' = -\beta SI, \quad (1a)$$

$$\frac{dE}{dt} = E' = \beta SI - \epsilon E, \quad (1b)$$

$$\frac{dI}{dt} = I' = \epsilon E - \alpha I, \quad (1c)$$

$$\frac{dR}{dt} = R' = (1 - f)\alpha I, \quad (1d)$$

$$\frac{dD}{dt} = D' = f\alpha I, \quad (1e)$$

where: S' is change in susceptible S is susceptible population,
 E' is change in exposed E is exposed population,
 I' is change in infected I is infected population,
 R' is change in resistant R is resistant population,
 D' is change in deceased D is deceased population.

and,

ϵ is the mean exposed period, expressed in inverse days.

α is the mean infective period, expressed in inverse days.

f is the fatality rate.

β is the infection rate proportionality constant, which quantifies new infectious contacts per infected person per day. With partial patient quarantine and tracing measures in place, the effective infection rate is assumed to approach the uncontrolled rate as some function of I . A binary operator is added for national quarantine measures.

$$\beta = (1 - Th) \times \frac{\beta_{max}}{1 + me^{nI}} \quad (2)$$

where:

T is a binary operator for national house-level quarantine.

h is effect of national house-level quarantine.

β_{max} is the contract factor with public awareness alone.

m & n are constants.

and I (as in indigo) is the infected population.

A simpler or more accurate estimate of the contact rate can certainly be substituted for that component. Time driven estimates may be fruitful, however the main driving component appears to be the number of people infected.

The desired effect of house-level quarantine and increased contact tracing is shown in Figure 2.

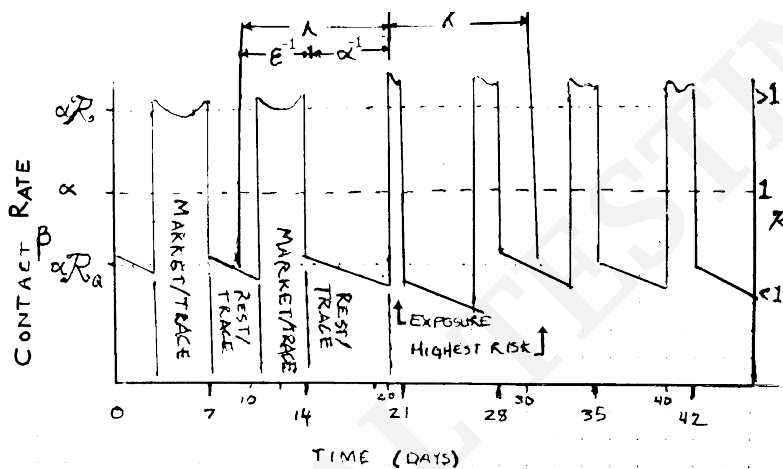


Figure 1: Hypothetical effect of intermittent *house-level* quarantine on the infection rate and the *basic reproduction ratio*, λ is the natural frequency of the system.

A substantial increase in contract tracing should cause a dramatic increase in reported cases, this increase should not to be confused with an instantaneous increase in infections (from individuals exposed five days prior). The converse should also be true. That is, if increased contact-tracing reports fewer cases than expected, it would provide evidence that enhancing surveillance reduces effectiveness.

Lockdown measures may increase the contact rate on non-quarantine days, due to a higher level of economic activity. The system has a natural frequency equal to the exposed period plus the infective period. Periods of activity and quarantine should be staggered across the natural frequency to avoid erratic behavior in the underlying system. A weekly schedule is shown on the timeline of Figure 2.

Solving for h may show the effect of house-level quarantine on the contact rate. If the results are encouraging, a quarantine schedule may be developed to minimize the ultimate size of the epidemic, as well as the duration. Even if $\mathcal{R}_{effective}$ does not fall below 1, mitigating the rate of infection, as soon as possible, increases time for development of treatments and vaccines.

A reliable estimate of β_{max} should be developed to evaluate the time-scale of risks posed by ‘wait-for-help’ strategies.

6 Initial Results

Assuming an infective period of 5.3 days, and an exposed period of 5.61 days, the differential equations were fit to total recovered individuals and total reported cases for Sierra Leone using sum of squared error analysis.

parameter	value
$\mathcal{R}_{free}$	1.81
β_{max} (total)	$4.8e - 8$
β_{max} (unit)	0.29
m	0.95
n	0.011

Table 2: Optimized parameters quantifying breakdown of control measures.

The regression fit is quite sensitive. Particularly, the β_{max} is the limit of the curve which can only be expected to be approached, but not reached. Using estimate cases may lead to a horrific results. As reporting mechanisms approach capacity, there is likely to be a breakdown in reporting accuracy. Estimates of $\mathcal{R}_{free}$ from literature indicate the rate may in fact be much higher, and even extraordinary measures may be too late.

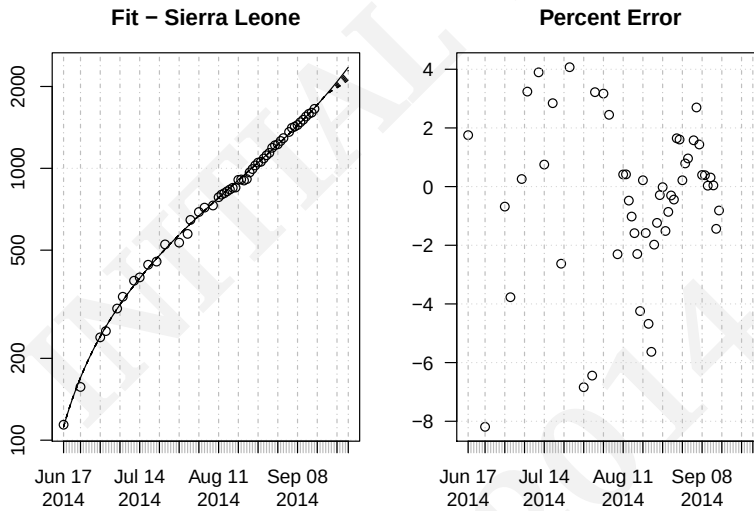


Figure 2: Fit on case and recovery data to Sept 13.

The assumed effect of combined national reporting, awareness and house level quarantine at given intervals are shown in Figures 3, 4 & 5. The effect relies on being paired with conventional contact intervention measures, such as those which have been proven successful in more undeveloped countries.

The true effect can be estimated roughly two weeks after measures are taken. Quarantine measures taken in reaction to super-spreading events (caused by a lack of security) and implemented without contact intervention do not provide a reliable source of

data for the effectiveness of the proposed course of action, although they may furnish some insight into the uncontrolled rate of spread.

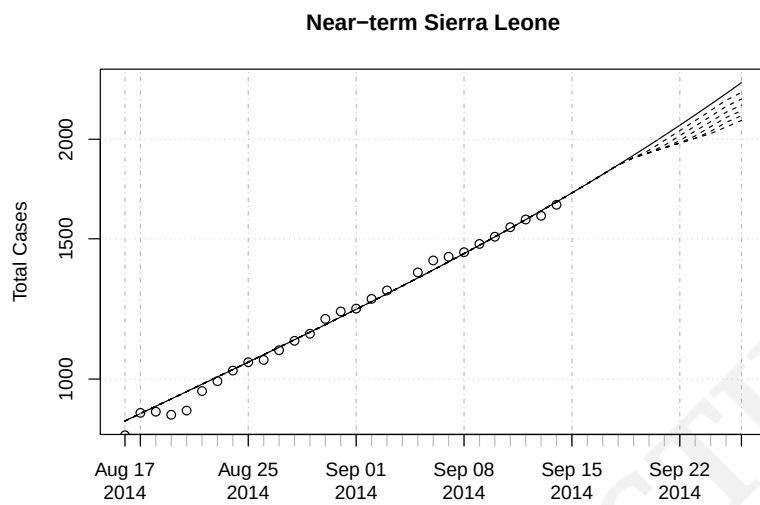


Figure 3: Effect of 50% effective national quarantine regiment. Dashed lines show 1,2...6 days of quarantine per week.

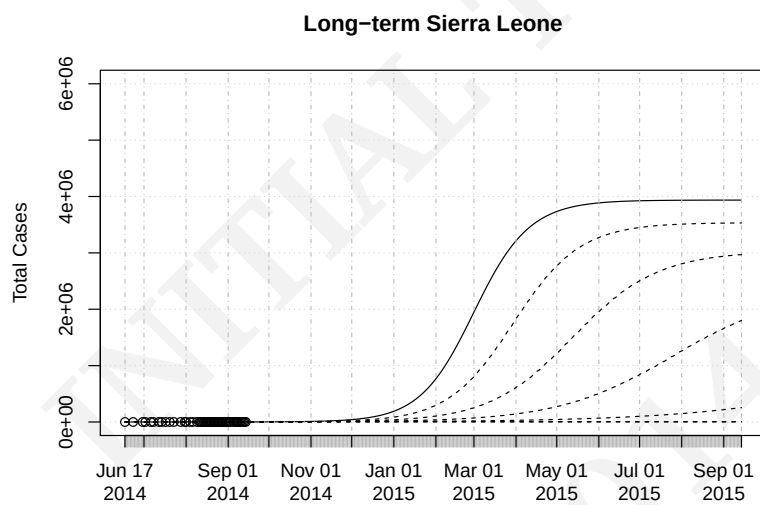


Figure 4: Effect of 50% effective national quarantine regiment. Dashed lines show 1,2...6 days of quarantine per week.

All models are inevitably wrong, the aim is to be less wrong, furnish useful insight and develop an effective tool for policy makers. What policies are implemented, and the manner of their implementation, lies with the individuals on the ground those that lead them.

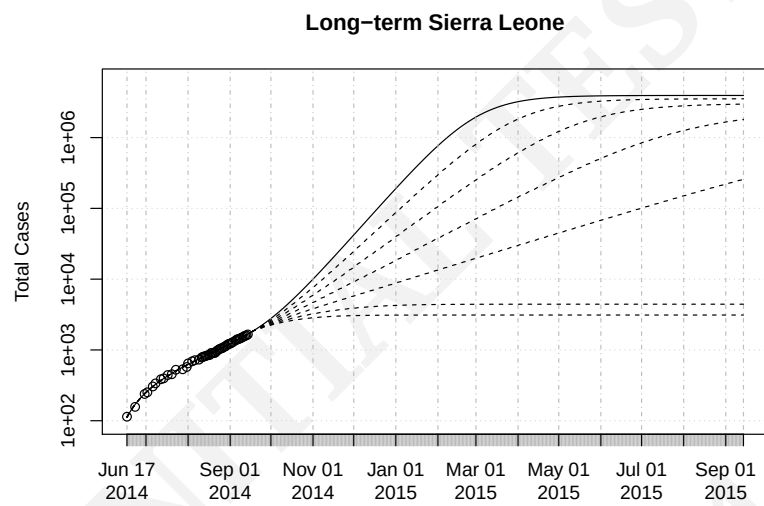


Figure 5: Effect of 50% effective national quarantine regiment. Dashed lines show 1,2...6 days of quarantine per week.

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Acronyms

ZEBOV	<i>Zaire Ebola virus</i>	2
EBOV	<i>Ebola virus</i>	3
MSF	Médecins sans Frontières	2
SEIHFR	<i>Susceptible-Exposed-Infectious-Hospitalized-Funeral-Resistant</i> .	3
VLP	virus like particles	4
NHP	non-human primates	4
GIS	Geographic Information System	5